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Invited critical review

Urinary liver type fatty acid binding protein in diabetic nephropathy

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ABSTRACT

Deterioration of diabetic nephropathy (DN) is largely determined by the degree of tubulointerstitial changes rather than the extent of histological changes in the glomeruli. Therefore, a tubular marker that accurately reflects tubulointerstitial damage may be an excellent biomarker for early detection or prediction of DN. Liver-type fatty-acid binding protein (L-FABP) is a 14 kDa small molecule that is expressed in the cytoplasm of human proximal tubules. *In vivo* experimental studies revealed that renal L-FABP gene expression was up-regulated by various stresses that cause tubulointerstitial damage, such as massive proteinuria, hyperglycemia, hypertension, ischemia and toxins, and that urinary excretion of L-FABP was increased. Recent clinical studies of patients with type 1 or type 2 diabetes demonstrated that urinary excretion of L-FABP derived from proximal tubules is a suitable biomarker for predicting and monitoring deterioration of renal function in DN. Moreover, therapeutic interventions with renoprotective effects reduced urinary L-FABP concentrations. Therefore, urinary L-FABP measured using the Human L-FABP ELISA Kit developed by CMIC Co., Ltd. (Tokyo, Japan) was confirmed as a newly established tubular biomarker by the Ministry of Health, Labour and Welfare in Japan in 2010. This review article summarizes the clinical significance of urinary L-FABP in DN.

Contents

1. Introduction

Diabetic nephropathy (DN) is the leading cause of chronic kidney disease (CKD), which ultimately progresses to end-stage renal failure and increases the risk of cardiovascular disease. Therefore, early diagnostic markers for predicting and monitoring the progression of DN are needed to enable the timely administration of the most appropriate protective treatments.

Tubulointerstitial injury has been suggested to have an important impact on the progression of DN [1]. Liver-type fatty-acid binding

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protein (L-FABP) is expressed in the proximal tubules of the human kidney and participates in fatty acid metabolism [2]. Results of animal studies of kidney disease showed that human *L-FABP* gene expression in the kidney was up-regulated and that urinary excretion of human L-FABP was increased by stress (e.g., urinary protein overload [3], tubular ischemia [4], tubular stretch [5], hyperglycemia [6], toxins [7,8] and hypertension [9] that causes tubulointerstitial damage. In a clinical study of patients with non-diabetic CKD, urinary excretion of L-FABP was found to correlate with the severity of tubulointerstitial damage [3] and with the rate of CKD progression [10]. Urinary L-FABP thus offers potential as a clinical marker to screen for kidney dysfunction and thereby to identify patients who are likely to experience deterioration of renal function in the future.

With respect to the relationship between urinary L-FABP and DN, increased urinary L-FABP is widely known to be associated with the severity of DN [11–15] and the progression of DN in future [11,14,16,17]. Furthermore, there have been numerous reports of intervention studies in which urinary L-FABP possesses response to renoprotective treatment [12,13,18–24]. This review summarizes recent findings on the clinical significance of urinary L-FABP in DN. Those findings showed that urinary L-FABP concentrations increased in parallel with the progression of DN and that high concentrations of urinary L-FABP presented a risk of progression of DN, of cardiovascular events and anemia.

2. Measurements of urinary L-FABP

To avoid variations that occur through differences in the ELISA kit used for measuring urinary L-FABP concentrations, only studies pertaining to the clinical significance of urinary L-FABP measured using the Human L-FABP ELISA Kit developed by CMIC Co., Ltd. (Tokyo, Japan) were reviewed [10]. In 2010, the Ministry of Health, Labour and Welfare approved the use of only this kit for diagnosis in clinical practice in Japan. The urinary L-FABP concentration was expressed as the ratio of the urinary L-FABP concentration to the urinary creatinine concentration in all studies.

To determine control reference values for urinary L-FABP in spot urine, 412 healthy volunteers were examined [11]. The mean value of urinary L-FABP in spot urine, determined from the logarithmic-transformed data (log L-FABP), was 1.6 μg/g creatinine, with individual values ranging from 0.3 μg/g creatinine (mean − 2 SD) to 8.4 μg/g creatinine (mean + 2 SD).

3. Dynamics of renal L-FABP in DN from an experimental study

Because renal L-FABP is not endogenously expressed in the kidneys of mice, we generated human L-FABP chromosomal transgenic (Tg) mice and evaluated the dynamics and pathophysiological role of renal L-FABP [25]. With regard to DN, a streptozotocin (STZ)-induced diabetic model, which has type 1 diabetes, was used and tubulointerstitial damage was provoked [6]. Our findings revealed that renal human L-FABP gene expression was up-regulated (around 9-fold increase) and that urinary excretion of human L-FABP increased (around 9-fold increase) in the STZ-induced diabetic Tg mice compared with control mice at 8 weeks after STZ injection. From the observation of lipid accumulation in human proximal tubules in DN [26], it could be suggested that lipid or peroxidation product generated in the proximal tubules of DN might promote the up-regulation of renal L-FABP expression. Our Tg mice were generated by microinjections of the genomic DNA of human L-FABP including its promoter region; therefore, it is possible for the transcription of the human L-FABP gene in the Tg mice to be regulated in the same mode as in humans. The dynamics of human L-FABP in the experimental diabetic model might mimic those under pathological conditions in humans as reported in the clinical cross-sectional studies described below.

4. Clinical significance of urinary L-FABP in diabetic nephropathy

4.1. Cross-sectional studies (Table 1)

Two studies of type 1 diabetes [13,14] and three studies of type 2 diabetes [11,12,15] reported on the relationship between urinary L-FABP concentrations and the severity of DN. In type 1 diabetes, urinary L-FABP concentrations increased with the progression of DN and were higher in normoalbuminuric patients than in control subjects [13,14]. These results indicated that urinary L-FABP accurately reflected DN severity and may be a suitable biomarker for early detection of DN.

Why urinary L-FABP concentrations increased in patients with normoalbuminuria in comparison with control subjects is not yet known. It is possible that in the normoalbuminuric phase chronic hyperglycemia may provoke microvascular damage [27], leading to tubular hypoxia and finally tubulointerstitial damage. Tubular hypoxia activates hypoxia inducible factor-1 (HIF-1) [28], which binds the hypoxia responsive element in the promoter region of the L-FABP gene, up-regulates the gene expression of L-FABP and promotes urinary excretion of L-FABP [4]. Therefore, chronic hypoxia could have induced an increase in urinary L-FABP in the normoalbuminuric phase.

In type 2 diabetes, urinary L-FABP concentrations increased with the progression of DN [11,12,15] and reflected DN severity. In one report, urinary L-FABP levels were significantly higher in patients with normoalbuminuria than in control subjects [11]. However, among clinical studies of type 2 diabetes, urinary L-FABP concentrations were comparable between patients with normoalbuminuria and those with microalbuminuria [15] and between patients with normoalbuminuria and control subjects [12]. In the study of Suzuki et al. [15], the frequency of measuring urinary albumin was not described and the urinary L-FABP concentration in patients with microalbuminuria (mean value, 5.2 μg/g creatinine [15]) was lower than that reported in other studies (mean value, 8.6 μg/g creatinine [11] or 19.6 μg/g creatinine [12]). Possibly the frequency of urinary albumin measurements was insufficient and the diagnosis of DN severity according to the urinary albumin concentration led to over-diagnosis. Therefore, patients with normoalbuminuria might have been entered by mistake into the microalbuminuria group, resulting in a lower median or average urinary L-FABP concentration in the microalbuminuria group. In the study of Nakamura et al. [12], urinary L-FABP in the control subjects (mean value, 5.8 μg/g creatinine) was higher than that reported in another study (mean value, 1.6 μg/g creatinine [11]) and was almost the same as that of microalbuminuric patients in another study (mean value, 5.2 μg/g creatinine [15]). It is possible that the criteria for the selection of control subjects was not sufficiently strict and that the number of control subjects was too small [12]. Because DN developing from type 2 diabetes is known to be a multifactorial disorder that can deteriorate through the presence of various factors such as hyperglycemia, hypertension, obesity and hyperlipidemia and since type 2 diabetes patients are more heterogeneous than type 1 diabetes patients, identical results might not be obtainable in clinical studies of type 2 diabetes. Furthermore, cut-off values for urinary L-FABP for detection of normo- or microalbuminuria have not been investigated yet. These points should be considered in future clinical studies.

Anemia induces tubular hypoxia and leads to the progression of DN [29,30], and is frequently observed even in diabetic patients in the early stage of DN. These patients not only experience a fast decline in renal function, but also increased mortality and morbidity [31,32]. The correlation between urinary L-FABP and anemia has been studied [33]. The superiority of urinary L-FABP in comparison with urinary kidney injury molecule (KIM-1) [34] and urinary N-acetyl-b-glucosaminidase (NAG), known as another tubular damage marker, was emphasized. That research involved 130 type 2 diabetes patients with albuminuria and creatinine clearance more than 60 mL/min and 40 healthy control subjects [33]. Only urinary L-FABP was correlated with the hematocrit ($r = -0.188$, $p = 0.032$), hemoglobin ($r = -0.190$, $p = 0.030$) and anemia based on the WHO definition ($r = -0.266$, $p = 0.002$), but not

Table 1
Characteristics of cross sectional studies of diabetic nephropathy (DN).

Type of diabetes	No. subjects Control/DM	Definition of DN severity (No. stages)	Kind of urine sample	Change in urinary L-FABP level	Year, Ref No.
Relationship between urinary L-FABP and DN severity					
Type 1 diabetes	57/148	Levels of urinary albumin determined in 3 consecutive 24-h urine samples (3 stages)	First morning urine	Normoalbuminuria group > *Control group. Increase with increase in urinary albumin levels.	2009, 13
	208/2454	Levels of urinary albumin determined in 3 consecutive 24-h urine samples (3 stages)	24-h urine	Normoalbuminuria group > *Control group. Increase with increase in urinary albumin levels.	2013, 14
Type 2 diabetes	0/356	Levels of urinary albumin determined in first morning urine and serum creatinine (4 stages)	First- morning urine	Increase with increase in urinary albumin levels and with renal dysfunction. Normoalbuminuria microalbuminuria. Comparison with control group not reported.	2005, 15
	20/58	Levels of urinary albumin determined in 24-h urine and serum creatinine samples (4 stages)	24-h urine	Normoalbuminuria group Control group. Increase with increase in urinary albumin levels and with renal dysfunction.	2005, 12
	412/140	Levels of urinary albuminuria determined in 3 consecutive spot urine and serum creatinine samples (4 stages)	Spot urine	Normoalbuminuria group > *Control group. Increase with increase in urinary albumin levels and with renal dysfunction.	2011, 11
Relationship between urinary L-FABP and anemia					
Type 2 diabetes	40/130	Levels of urinary albumin and creatinine clearance determined in 3 consecutive 24-h urine samples.	24-h urine	Close relation between urinary L-FABP levels and chronic anemia.	2010 33

Ref, Reference. >*, significantly higher ($p < 0.05$).

urinary KIM-1 and urinary NAG. Patients with diabetes and anemia ($n = 30$) had significantly higher urinary L-FABP than non-anemic diabetes patients ($n = 100$). In groups formed according to tertiles of increasing urinary L-FABP concentrations, a stepwise increase in urinary L-FABP was associated with decreasing hemoglobin levels. Furthermore, in multivariable adjusted logistic regression analysis to identify independent factors for the increasing urinary L-FABP concentrations, anemia (odds ratio, 6.06; 95% CI: 1.652–22.232; $p = 0.039$) was a significant risk factor for increased urinary L-FABP excretion. The authors concluded that urinary L-FABP was a highly sensitive marker of a renal microcirculation disorder induced by anemia, which is a factor in the progression of DN. Two other studies support this conclusion; one reported that in patients with chronic renal failure, administration of erythropoietin decreased urinary L-FABP along with an increase in hemoglobin [35], and the other showed that in kidney transplant recipients, urinary L-FABP concentrations increased in parallel with decreased peritubular capillary blood flow, which was shown using non-invasive CCD video recording [4].

Although the mechanism by which anemia increased urinary L-FABP excretion was not revealed [33], it was speculated that tubular hypoxia induced by anemia up-regulates the gene expression of L-FABP and promotes the urinary excretion of L-FABP. In future, when new treatments for kidney disease that improve tubular hypoxia are developed, urinary L-FABP will be a useful target for therapeutic regimens.

4.2. Prospective observational follow-up studies (Table 2)

Of prospective observational studies of patients with diabetes, three studies of type 1 diabetes [14,17,36] and two studies of type 2 diabetes [11,16] were performed. In type 1 diabetes, Cox regression analysis indicated that urinary L-FABP was an independent predictor of progression from normoalbuminuria in two studies [14,17] and in one study of the progression to macroalbuminuria over a period of more than 6 years [14]. In microalbuminuric patients with type 1 diabetes, univariate analysis (odds ratio, 1.49; 95% CI: 1.20–1.85, $p < 0.001$) and multivariate analysis without urinary albumin (odds ratio, 1.40; 95% CI: 1.10–1.79, $p = 0.006$) showed that L-FABP was a predictor of progression to microalbuminuria [14]. However, when urinary albumin was added as a variable in Cox regression analysis, an increase in urinary L-FABP was not associated with a higher risk of progression to microalbuminuria (odds ratio, 0.67; 95%: CI 0.48–0.95, $p = 0.027$) [14]. One possibility for this result is that the urinary L-FABP concentrations were strongly correlated with the urinary albumin concentrations and that each of these two parameters became a confounding factor in Cox regression analysis. Regarding the merit of measuring urinary L-FABP in addition to urinary albumin in type 1 diabetes, the area under the receiver operating characteristic curve (AUC) for predicting the progression of DN at each stage of DN was studied [14]. Although predicting the progression to macroalbuminuria or end stage renal failure using urinary L-FABP together with urinary albumin appears to have no clinical benefit, the AUC when using both urinary L-FABP and urinary albumin (AUC = 0.786) to predict the progression to microalbuminuria was higher than with urinary albumin alone (AUC = 0.778, $p = 0.092$) in patients with normoalbuminuria. Taken together, in type 1 diabetes, urinary L-FABP may be a useful biomarker for predicting progression from the earliest stage of DN and there may be an advantage in measuring urinary L-FABP in addition to urinary albumin.

In one study in which the correlation between urinary L-FABP and a decline in the glomerular filtration rate (GFR) in type 1 diabetes patients with macroalbuminuria was evaluated for a short duration (3 years), urinary L-FABP was not predictive of a decline in GFR [36]. An observational study with a longer follow-up period is needed to clarify this point.

The two studies of this issue in type 2 diabetes were performed in Japan [11,16]. One study showed that urinary L-FABP was an independent predictor of progression of DN, which was defined as advancement to the next higher stage in patients with all stages of DN without the requirement of dialysis or kidney transplantation; analysis of a subgroup with an estimated GFR (eGFR) >60 ml/min per 1.73 m^2 showed results consistent with the former result [11]. A high urinary L-FABP value at study entry (than upper limit of reference value of urinary L-FABP, 8.4 μg/g creatinine) was a higher risk factor for progression of DN than the presence of albuminuria at entry [11]. Although without significance ($p = 0.45$), the AUC for predicting the progression of DN by urinary L-FABP (AUC = 0.762) was higher than that by urinary albumin (AUC = 0.675) in the subgroup with an eGFR >60 ml/min per 1.73 m^2 [11]. Furthermore, when the primary endpoint was defined as the requirement for dialysis or a cardiovascular event in patients with normoalbuminuria or microalbuminuria, the incidence rate of the primary endpoint increased in a stepwise manner with increases in urinary L-FABP by Cox regression analysis (odds ratio, 2.16; 95% CI: 1.23–3.79) [16]. Although urinary L-FABP also may be an appropriate biomarker for predicting progression from the earliest stage of DN or to cardiovascular events in type 2 diabetes, there have been few studies from Japan and none elsewhere on this topic. Further studies are needed to reconfirm the potential of urinary L-FABP as a predictor of the progression of DN or of cardiovascular events.

Table 2
Characteristics of prospective observational follow-up studies of diabetic nephropathy (DN).

Type of diabetes	No. subjects (follow-up periods: year)	Primary endpoints	Baseline of DN severity	Cox regression analysis using progression of DN, Adjusted odds ratio (95%CI)	Year, Ref No.
Type 1 diabetes	165 (18)	Increase in urinary albumin levels determined in 24-h urine sample	Normo-albuminuria	2.28 (1.14–4.58)	2010, 17
	356 (6–10)	Increase in urinary albumin levels determined in 24-h urine and requirement of dialysis or kidney transplantation	All stages of DN without requirement of dialysis or kidney transplantation	Progression from normoalbuminuria 2.97 (1.50–5.90) Progression from microalbuminuria 0.67(0.48–0.95) Progression from macroalbuminuria 1.17 (1.10–1.24)	2013, 14
	63 (3)	Decline in GFR measured as plasma clearance of an intravenous injection of ^{51}Cr-EDTA.	Macroalbuminuria with GFR >60 ml/min per 1.73 m^2	Not reported. Not predictive of decline in GFR. All patients 7.29 (2.43–21.88)	2011, 36
Type 2 diabetes	104 (4)	Increase in urinary albumin levels determined in 3 consecutive spot urine and serum creatinine samples	All stages of DN without requirement of dialysis or kidney transplantation	Patients with eGFR >60 mL/min per 1.73 m^2 9.46 (2.24–39.92)	2011, 11
	618 (11–15)	Requirement of dialysis or cardiovascular events	Normo- and microalbuminuria with serum creatinine <1.0 mg/dL	2.16 (1.23–3.79)	2013, 16

Ref, Reference; GFR, glomerular filtration rate; eGFR, estimated GFR.

4.3. Interventional studies (Table 3)

Two studies of type 1 diabetes reported changes in urinary L-FABP by intervention with angiotensin converting enzyme inhibitor (ACE-I) [13] or aldosterone blockade [24]. Using ACE-1 [13] or aldosterone blockade [24], urinary L-FABP concentrations decreased [13] or tended to decrease [24] along with decreases in urinary albumin concentrations. In type 2 diabetes, two studies using a statin [12,18], one using antidiabetes drugs [23], two using a calcium channel blocker [19,22], one using a blocker of the renin-angiotensin system [20,21], and one using a blocker of the renin-angiotensin system and a calcium channel blocker [20] were reported from Japan. Results showed that urinary L-FABP decreased through the use of various renoprotective interventions and that urinary L-FABP had a drug response. Urinary L-FABP may be useful as a surrogate marker for the effectiveness of therapy.

Table 3
Characteristics of intervention studies of diabetic nephropathy (DN).

Type of diabetes	No. subjects (intervention periods: months)	Content of treatment (generic name, dose/day)	Primary endpoints	Changes in urinary L-FABP	Year, Ref No.
Type 1 diabetes	48 (8)	ACE-I (lisinopril, 20 mg, 40 mg, 60 mg)	Changes in urinary albumin.	Reduction in urinary L-FABP was associated with changes in urinary albumin, but not with dose of lisinopril.	2009, 13
	21 (2)	Aldosterone blockade (spironolactone, 25 mg)	Changes in urinary albumin.	Urinary L-FABP levels tended to decrease after spironolactone treatment along with reduction of urinary albumin.	2012, 24
Type 2 diabetes	20 (12)	Statin (pitavastatin, 1 mg)	Changes in urinary albumin.	Urinary L-FABP levels decreased after pitavastatin treatment along with reduction of urinary albumin.	2005, 12
	104 (6)	Statin (rosuvastatin, 2.5 mg)	Changes in serum creatinine, eGFR, serum cystatin C and urinary albumin.	Urinary L-FABP levels decreased after rosuvastatin treatment along with reduction of urinary albumin. Although serum creatinine and eGFR did not significantly decrease, serum cystatin C levels significantly decreased.	2011, 18
	68 (12)	Antidiabetes drugs (pioglitazone 30 mg, glibenclamide 5 mg, voglibose 0.6 mg, nateglinide, 270 mg)	Changes in urinary albumin.	Urinary L-FABP levels decreased after pioglitazone treatment along with reduction in urinary albumin.	2006, 23
	45 (12)	Calcium channel blocker (azelnidipine, 8 mg, 16 mg)	Changes in urinary albumin.	Urinary L-FABP levels decreased after azelnidipine treatment dose-dependently along with reduction in urinary albumin.	2008, 22
	67 (6)	Calcium channel blocker (azelnidipine, 8 mg, 1 6 mg, amlodipine, 2.5 mg, 5 mg)	Changes in urinary albumin, serum creatinine and eGFR.	Urinary L-FABP levels decreased after azelnidipine treatment along with reduction in urinary albumin. Serum creatinine and eGFR did not significantly decrease.	2011, 19
	68 (12)	ARB (losartan, 100 mg, candesartan, 12 mg, olmesartan, 40 mg, telmisartan, 80 mg)	Changes in urinary albumin and 24-h Ccr.	Urinary L-FABP levels decreased after ARB treatment along with reduction in urinary albumin. Ccr did not decrease.	2010, 21
	64 (6)	Renin inhibitor (aliskiren, 150 mg, 300 mg,) Calcium channel blocker (amlodipine, 5 mg, 7.5 mg)	Changes in serum creatinine, eGFR, and urinary albumin.	Urinary L-FABP levels decreased after aliskiren or amlodipine treatments along with reduction in urinary albumin. serum creatinine and eGFR did not significantly decrease.	2012, 20

Ref, Reference; ACE-I; angiotensin converting enzyme inhibitor; ARB; angiotensin II receptor blocker; Ccr; creatinine clearance; eGFR; estimated glomerular filtration rate.

5. Conclusion

Although studies in which the advantages of urinary L-FABP compared to the existing clinical markers have been few [11,14], the clinical relevance of urinary L-FABP as a predictor of progression of DN [11,14,17], of requirement for dialysis or cardiovascular events [16] and of anemia [33], or as a target for therapeutic regimens [12,13,18–24] was demonstrated by some clinical studies. However, tubular markers, including urinary L-FABP, did not predict a decline in GFR in patients with DN with overt nephropathy in one study [36]. Furthermore, because the progression of DN was defined as an increase in urinary albumin concentrations until progression to end stage renal failure, it may be difficult to determine that the potency of urinary L-FABP for diagnosis or prediction of progression of DN is higher than that of urinary albumin. Therefore, further large multicenter clinical studies on large populations are expected to be performed in future to reconfirm the clinical usefulness of urinary L-FABP on another important endpoint apart from an increase in the urinary albumin level, such as prediction of the need for dialysis, cardiovascular events and death in each stage of DN severity.

Conflict of Interest

Takeshi Sugaya is the senior director and senior scientist of CMIC Co. Ltd. (Tokyo, Japan), a company that produced the kits for L-FABP analysis. No other potential conflicts of interest relevant to this article are reported.

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